Basal Ganglia

Introduction

The basal ganglia are a group of ganglia (actually they are nuclei, being clusters of neurons in the central nervous system, but they have been and will always be called the basal ganglia) in the deep brain. The basal ganglia have a very complex interaction with each other, which either enables or prevents movement. More accurately, this group is involved in complex motor movements that require coordinating muscles to contract and relax quickly, such as using a pen to write a letter of the alphabet. The basal ganglia are an accessory motor system that functions not by itself but rather in close association with the cerebral cortex. In fact, the basal ganglia receive most of their input signals from the cortex (from the **premotor cortex**) and return almost all their output signals back to the cortex (in the **primary motor cortex**).

If we dissect just one input, the story goes a little something like this. The premotor cortex has an idea and wants to move a muscle. When it's a simple movement, the premotor cortex creates a mirror image of what the primary cortex will do, passes that to the primary cortex, and the movement happens. For complex movements, many decisions must be made at once. The premotor cortex has too much planning to do, so it asks the basal ganglia for help. The basal ganglia process the idea, then pass the message on to the primary motor cortex. The premotor cortex has an idea but doesn't have the computational power to make sure it is a good idea. So it relies on the computational power of the basal ganglia to make sure the idea is good, and then the primary motor cortex can work on sending out the order—move or don't move. Obviously, it is more complex than we're making it out to be. And this is only the initiation of movement. We haven't even talked about the cerebellum and its role in smoothing out movement yet.

A word of warning regarding the weird naming of structures in Neuroscience: just read. Don't try to figure this out. Ganglia are called nuclei, and depending on whom you're talking to, each nucleus gets a new collective name when it is combined with another. The **deep nuclei** are the **basal ganglia**.

The basal ganglia consist of the caudate nucleus, putamen, nucleus accumbens, and globus pallidus. All four of those things are nuclei. When the caudate nucleus and putamen are together, they are called the striatum. The caudate and putamen are also called the dorsal striatum because the nucleus accumbens is also the striatum, but it's the ventral striatum. The putamen and globus pallidus are together called the lenticular nucleus. And the one globus pallidus, which is either part of the lenticular nucleus or on its own, is divided into two structures—the globus pallidus interna and the globus pallidus externa.

The deep nuclei do much more than this motor business we are about to discuss. And so, here is what it takes to master this system, anticipate disease presentation, and keep yourself sane.

There are "six nuclei" that make up the "basal ganglia of movement": the striatum, globus pallidus externa (GP_{ext}), globus pallidus interna (GP_{int}), subthalamus, substantia nigra, and thalamus. When you see these next few figures, you may feel confused by this paragraph. When you get to "*Cables of Light*," you'll get it. This is a major oversimplification of the system and ignores anatomical relationships. For example, almost all motor and sensory nerve fibers connecting the cerebral cortex to the spinal cord pass through the space that lies between the major masses of the basal ganglia, the caudate nucleus and the putamen. That thing—all sensory and motor nerves—is the internal capsule. The goal is to prepare you to comprehend Parkinson's disease and its management. Mastering everything the basal ganglia do isn't the point.

The Actual Deep Nuclei and Surrounding Structures

We are absolutely going out of the way to show you what the deep nuclei are and how they are conceptually related, radiologically and on sections of cadaveric brains. Then we're going to ask you to ignore them. We want you to feel confident touring around this region of the deep brain, but also don't want you to feel pressured to map the deep nuclei over and over again until you get them correct from memory. Our intent is to demystify the subject, freeing your mind to focus on the regulation of movement.

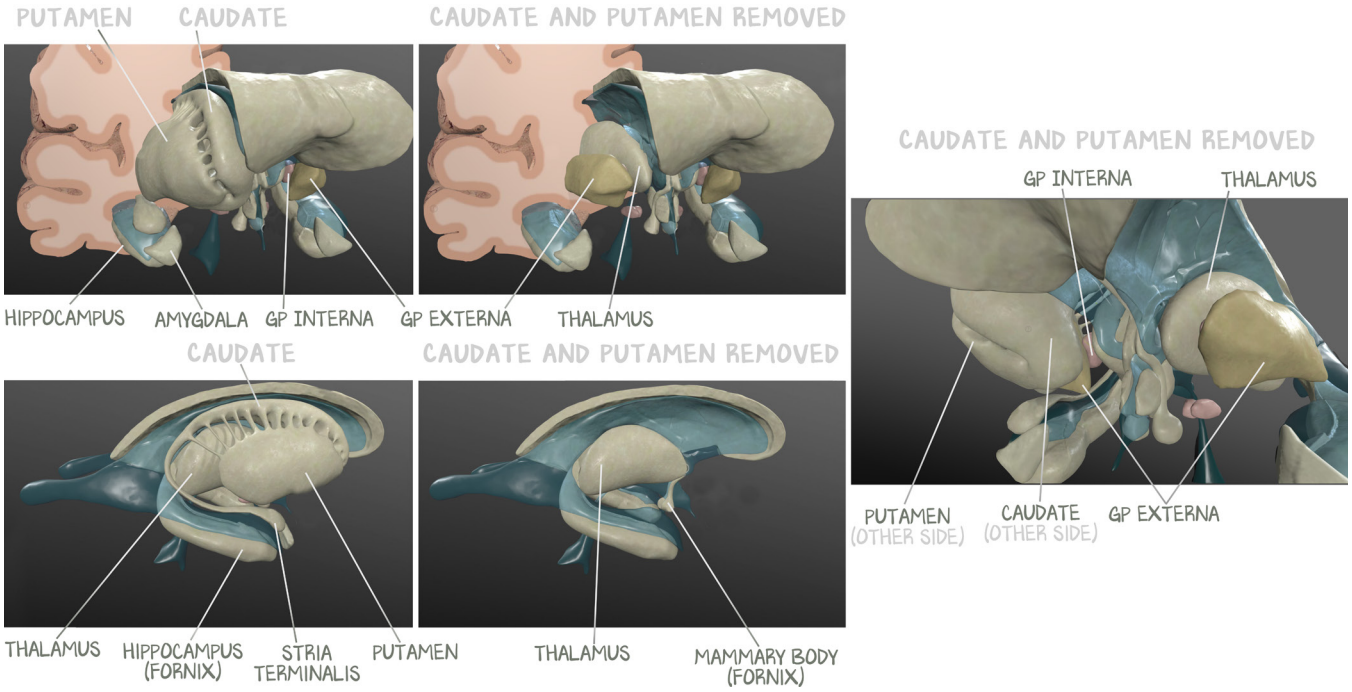

Figure 5.1: The Ganglia Modeled
This three-dimensional model demonstrates the basal ganglia in relation to the ventricles and corpus callosum. It is actually fairly difficult to visualize the different deep nuclei from any particular angle. The most important function of this model is to demonstrate their disk-like appearance—thin slices in the coronal plane, but elongated discs in the axial plane. The caudate nucleus assumes a similar shape to that of the lateral ventricle, with its head most anterior and its tail, the stria terminalis, above the inferior aspect of the lateral ventricle. The caudate nucleus is attached to the putamen through stingy connections. The putamen is the most lateral nuclei. From the outside in, the putamen is removed to reveal the globus pallidus externa (GP externa), then the globus pallidus is removed to reveal the globus pallidus interna. The most medial nucleus is the thalamus, each thalamus flanking the midline third ventricle. Other nearby structures—the fornix, hippocampus, and amygdala—are labeled, and then some others aren't—namely the hypothalamus. Notice also that the texture of the ventricles has been changed from what you saw in Cortex #3: *The Flow of CSF-Ventricles and Sinuses*. The choroid plexus is not depicted to make visualizing the nuclei easier.

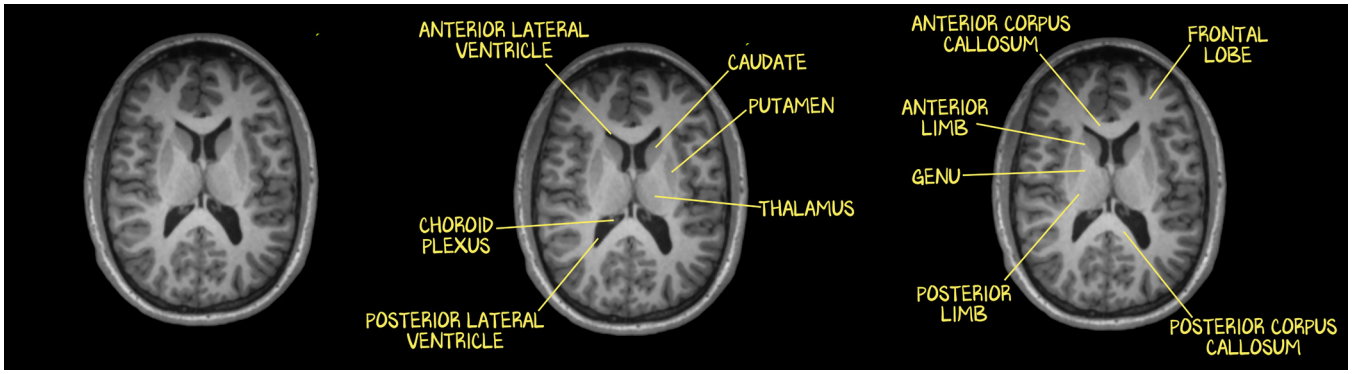

Figure 5.2: The Radiographic Ganglia
Radiologically, the easiest way to visualize the basal ganglia is with a T1-weighted axial MRI. At the top of the image is the frontal lobe, at the bottom is the posterior. The first image is unlabeled so you can track back and forth between the labels. The most medial nucleus is the thalamus (one on each side), the nucleus adjacent to the lateral ventricles is the caudate, and the most lateral nucleus is the putamen. Distinguishing the putamen from the globus pallidus is very difficult on MRI.

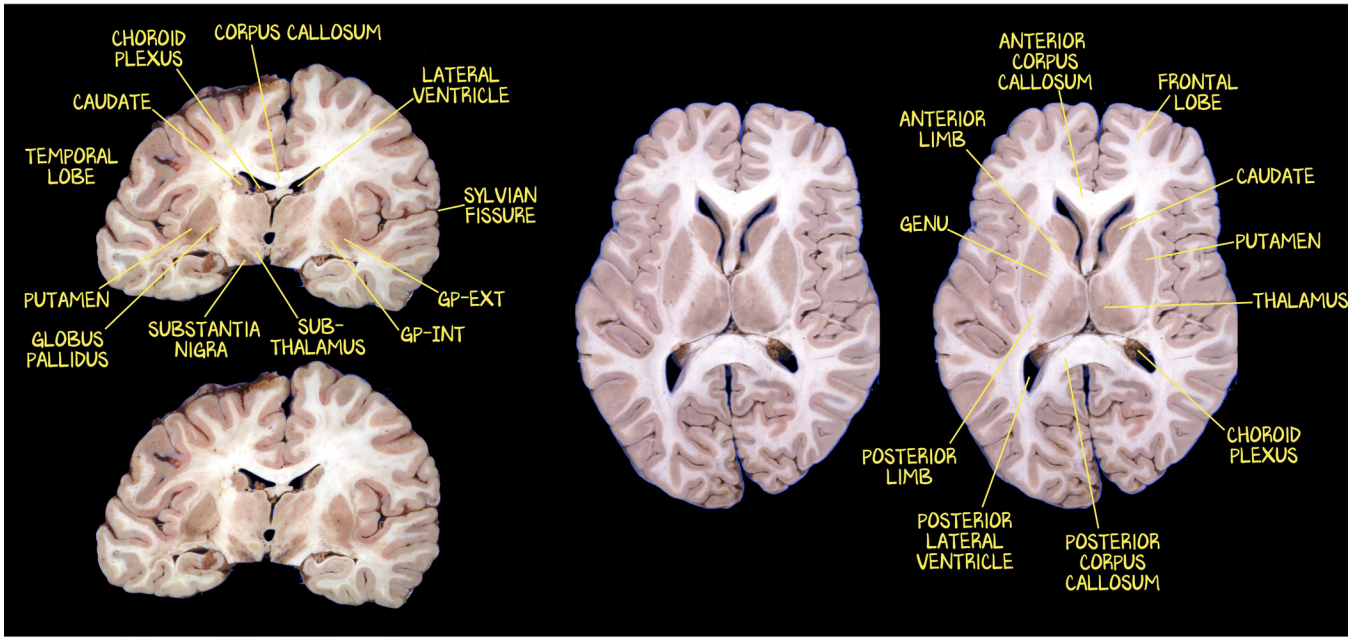

Figure 5.3: The Cadaveric Ganglia
On gross examination, the grey matter of the nuclei appears like the grey matter of the brain—brown. The axial section on the right demonstrates the relationship of the ganglia at the level of the internal capsule—the band of white matter that runs between the caudate and putamen (anterior limb) and between the putamen and thalamus (posterior limb). You'll hear more about the internal capsule in the Motor and Sensory Tracts island that follows this one. Again, the caudate is adjacent to the lateral ventricles, the putamen is the most lateral, and the thalamus the most medial. On the coronal section on the left, there is a better visualization of the differentiation between the globus pallidus externa (GP_{ext}), globus pallidus interna (GP_{int}), and putamen. Also visualized are the nuclei of the midbrain—the substantia nigra and the subthalamic nucleus (nuclei of the deep brain that you could not see in the other figures).

The Pathways of the Basal Ganglia

Layer 1: The Takeaway

What matters is the final output of the thalamus to the motor cortex—move or don't move. This is the most important thing related to Parkinson's disease: **dopamine activates the thalamus and therefore stimulates movement**.

Layer 2: The Cliff's Notes Version

There are two pathways: direct and indirect. The **direct** pathway results in the **disinhibition** of the **thalamus**, and therefore allows **movement**. It does so through dopamine from the **substantia nigra**. The **indirect** pathway results in the **inhibition** of the thalamus through **acetylcholine**, which prevents movement. Thus, there is a balance between go (dopamine) and don't go (acetylcholine).

Layer 3: The Painful Reality

The true story is stupefyingly complex. We're going to tell the story of the direct pathway first (if you want to just skip this paragraph, you may) to show you how impossibly complicated it is to explain in scientific terms. The cortex sends a signal to the striatum. There, the striatum is stimulated and sends projections to the GP_{int} and substantia nigra. We follow the GP_{int} arm first. The GP_{int} sends an inhibitory signal to the thalamus, which prevents movement. The striatum sends an inhibitory signal to the GP_{int}. With GP_{int} inhibited, the thalamus is disinhibited, allowing movement. Back to the striatum and its projection to the substantia nigra. The substantia nigra sends a direct inhibitory signal to the thalamus. The striatum sends an inhibitory signal to the substantia nigra, which therefore disinhibits the thalamus and allows movement. Here's where it gets really tricky. The substantia nigra has projections to the striatum that are stimulatory. That is the dopamine signal that is required for the striatum to activate the GP_{int} when instructed by the cortex. That same dopamine signal also inhibits the striatum's inhibitory projection to the substantia nigra. Here's the takedown. When the cortex tells the basal ganglia it wants to move, both the cortex projections and substantia nigra projections promote the disinhibition of the thalamus by inhibiting GP_{int}. At the same time, the same substantia nigra projection and cortical stimulus simultaneously halt that substantia nigra projection and the inhibitory projection to the thalamus. This usually goes over poorly because it is so confusing. And this is only the direct pathway. Adding on the indirect pathway only gets worse. Instead, we came up with a visual exercise that makes it far easier.

No image here to help with that paragraph. We want you to do the visual exercise first.

Layer 4: Cables of Light

Imagine this setup: Each of the structures is a building. Imagine a massively wide structure far off in the distance, hundreds of stories high. That is the thalamus. There is a much smaller version of that structure in the middle of the thalamus and a wee bit closer to you. That is subthalamus. To your right is a square-shaped concrete structure, like a parking garage. It's closer to you than the subthalamus, but way off to the right. That's the substantia nigra. To your left are two rounded structures really close to one another. The one closest to you obscures your sight of the other. The one that is closest to you is the GP_{ext}, and the one you can barely see is the GP_{int}. You are standing on an observation deck. You are standing on the striatum.

Cables run between these structures. Each cable is one of two kinds, either an inhibitor cable or a stimulator cable. A cable can be active or inactive. Inhibitor cables glow red when active, and are non-glowing and black when inactive. Stimulator cables glow green when active, and are also non-glowing and black when inactive.

See all those structures. Visualize them. Now envision four cables. The two at your feet run from the striatum to the GP_{int} and substantia nigra (one cable each) and are inhibitory cables. They glow red when active and fade to black when inactive. These cables are currently black, or inactive; they are not inhibiting anything yet. Two additional cables run from the GP_{int} and substantia nigra to the thalamus off in the distance. These cables are also inhibitory cables: red when active and black when inactive. Currently, the cables attached to the thalamus are glowing red—active—inhibiting the thalamus. The thalamus is therefore dark, inactive. And at your feet is a bucket full of dopamine. This is your starting point—everything is ready, in its resting state. At the striatum, you are where the cortex stands when the cortex wants to move.

Whatever your current construct of this exercise is, do not change it. Also, do not allow your knowledge of physics, electricity, action potentials, etc. to get in the way of the exercise. Anything that does happen, can happen in this construct. For those who need visual cues, we're going to show you one artist's depiction.

The cortex wants to move. In order to do so, it takes the dopamine bucket and dumps it all over the striatum. The striatum vibrates; white lights appear on the glass floor at the cortex's feet. The dark striatum cables begin to glow red, the illumination starting at the striatum and creeping outwards. **The cortex watches.** As the lengthening glows reach their targets (nearly simultaneously), each cable from the striatum intensely pulses red, signifying that they have hit their mark. The burst of red light gives way to a constant ruddy appearance. These cables will remain glowing red until the end of the show. Their pulse of red triggers the glowing red cables that connect the thalamus to the GP_{int} and substantia nigra to begin to inactivate—their red luminosity begins to fade to black, starting at the thalamus and retreating towards their source (GP_{int} and substantia nigra). With the fading of the red glow, the thalamus itself begins to hum and glow blue, the hum and hue growing more intense the farther the red glow withdraws—the inhibitory signal is inactivating. As the last flicker of red vanishes from the cables, the thalamus crackles with energy, and a blazing hot crack of blue light is sent to the cortex. The cortex moves.

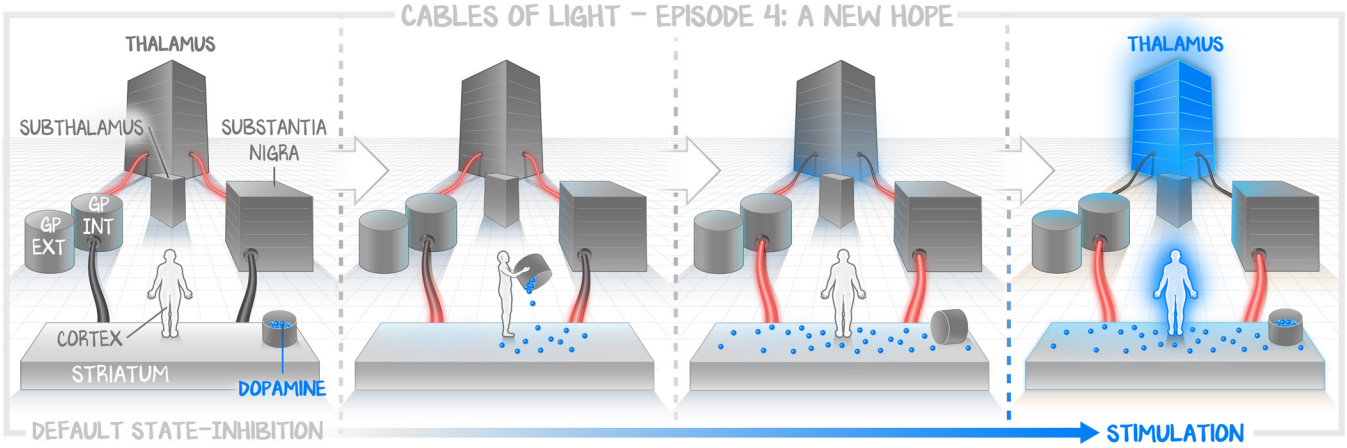

Figure 5.4: Cables of Light, Episode Four, A New Hope
A long time ago, in a galaxy far . . . We're pretty sure this isn't a trademark violation, but it's totally worth the payoff. The visualization of cables of light. In the default state, the thalamus is inhibited. The cortex moves by disinhibiting the thalamus, using dopamine to inhibit the inhibitors.

Dramatically long thought exercise. Why? What did you visualize? Four cables, each by turn red or black. In the **direct pathway**, everything is about the **disinhibition** of the thalamus. The cables are axons. The structures are nuclei. The glow emanating from the striatum towards the GP_{int} and the substantia nigra and the glow retreating from the thalamus towards each nucleus gives you the conceptual directionality of the neurons' projections. *"The striatum has neuron cell bodies with axons that project to either the substantia nigra or the globus pallidus interna. When the striatum is activated by dopamine, both sets of axons release a hyperpolarizing (inhibitory) neurotransmitter at the substantia nigra and the GPint. At baseline, the substantia nigra and GPint each have inhibitory axons that project to the thalamus. By inhibiting the inhibitors, the striatum disinhibits the thalamus."* It's more fun and just as accurate to use the cable image.

But alas, there is more. There is also an indirect pathway. The indirect pathway is how the basal ganglia are kept dormant, silent until the cortex wants to move. To fully understand this system, we have to add more cables.

Back to the resting point, Figure 5.4. Now envision the subthalamus with two cables, one to the GP_{int} and another to the substantia nigra. Both cables glow a bright green. These are active stimulatory cables. From the GP_{ext}, there is a dark cable running to the subthalamus. Lastly, there is a glowing red cable from the striatum to GP_{ext}.

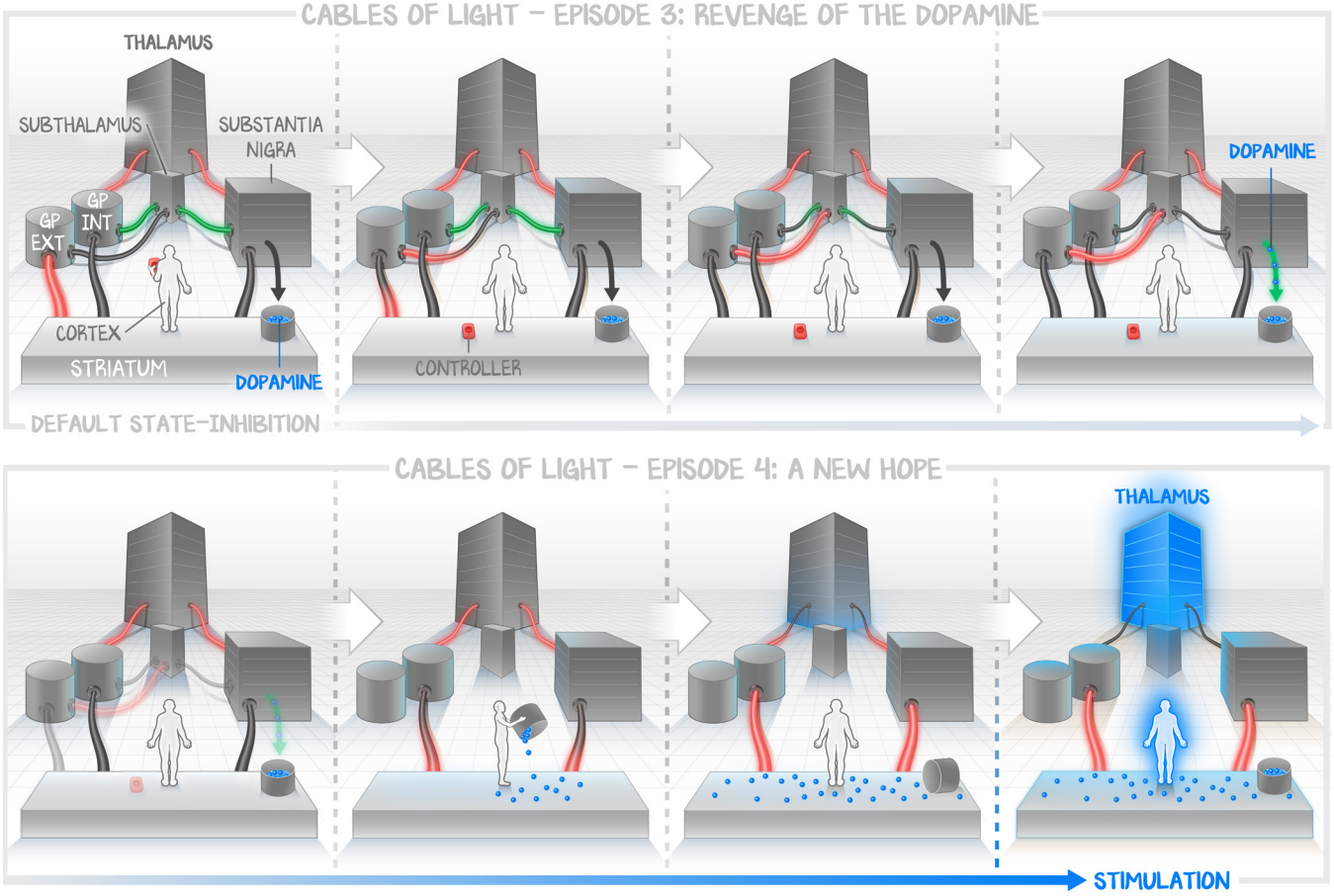

Figure 5.5: Cables of Light, Episode III: Revenge of the Dopamine
See the theme!? This story is a prequel to the last figure. The top row shows you the added complexity, but at the end of Episode III, it is almost the same (with only a little backstory added in) as the start of Episode IV. All you had to do was add in the GP_{ext} and subthalamus.

This system is turned on by the cortex through the **indirect pathway**. The cortex keeps its thumb on a receiver. As long as the button is pressed, there is no movement. When the cortex wants to move, it has to pick up the bucket of dopamine. That takes two hands. The cortex wants to move. It climbs onto the observation deck (striatum) and lets go of the controller. The red glow from the striatum to GP_{ext} fades, retreating towards the striatum. As it does, the cable from the GP_{ext} to the subthalamus begins to glow red, creeping out towards the subthalamus. The cortex bends down to pick up the bucket of dopamine. As the retreating red glow disappears at the striatum, the advancing red glow from the GP_{ext} reaches the subthalamus with a brief burst of red light, then sustains its red glow. As the flash of red light ends, the green glow in the cables to the substantia nigra and GP_{int} begins to fade, retreating towards the subthalamus. The cortex dumps the bucket of dopamine. Just as in the direct pathway, the red glow advances towards the substantia nigra and GP_{int}. Just as the green of the subthalamus's cables disappears, both cables from the striatum flash a bright red. The red glow of the cables from thalamus retreat towards the substantia nigra and the GP_{int}, just as in the last exercise.

The substantia nigra also serves as the dopamine machine. When stimulated by the subthalamus, it generates the dopamine that the cortex uses to make the light show start. Without dopamine, there is no way to start the show. Parkinson's is a disease of the substantia nigra, and has the symptom of bradykinesia (slowed movement).

Now you can have the thing that gets everyone confused. We've made it more understandable by using green arrows and red inhibitory bars, and we've added in the projections that we withheld in the thought exercise because they only make it more confusing.

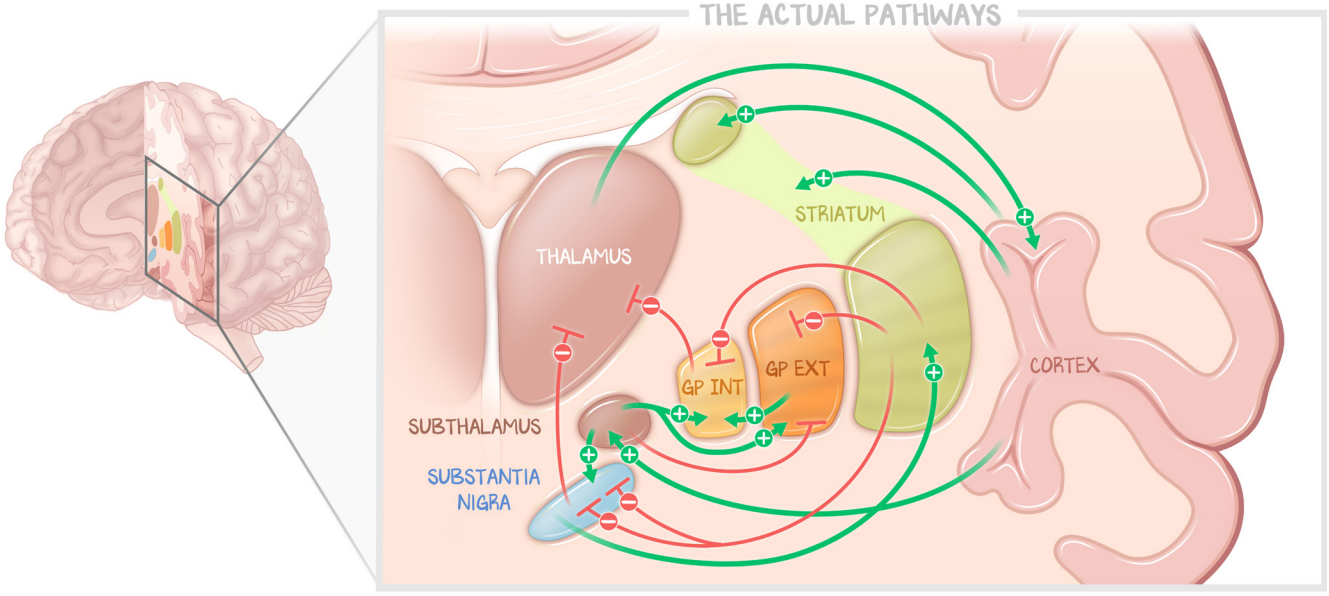

Figure 5.6: The Actual Pathways
The reason Dr. Williams created the Cables of Light was that he watched an expert—who was trying to help him understand these arrangements—mess it up three times. In a row. It wasn't because she wasn't an expert on the material or didn't know how to teach (she is actually very good at both the content and teaching). This was our illustrator's best attempt at making it manageable. If you doubt how complicated this can be, check out the image explanation on Wikipedia. Specifically, this one: https://en.wikipedia.org/wiki/Basal_ganglia#/media/File:Basal_ganglia_circuits.svg

Other Pathways that Dopamine Participates In

The **nigrostriatal pathway** was what we just discussed: dopamine goes from the substantia nigra (nigro-) to the striatum (-striatal). If you give a patient an antipsychotic that is a dopamine antagonist, it is possible to induce **Parkinsonism**. It will come as no surprise, then, that the treatment of Parkinson's disease centers on increasing dopamine activation.

The **mesolimbic pathway** involves connections from the ventral tegmental area (you don't know what this is yet) to the forebrain. It plays roles in emotion and reward and is responsible for the positive symptoms of schizophrenia. If you give a patient dopamine therapy, this pathway may elicit **hallucinations**.

The **mesocortical pathway** involves connections from the ventral tegmental area to the prefrontal cortex. It plays a role in cognition, executive function, and the negative symptoms of schizophrenia. Schizophrenia medications are antidopaminergic because both pathways involve overactivation of dopamine receptors; both the positive and negative symptoms of schizophrenia can be attributed to dopamine.

The **tuberoinfundibular pathway** has an atrocious name. Prolactin is released from the anterior pituitary, which is under the hormonal influence of the hypothalamus. The hypothalamus releases hormones into a specialized network of blood vessels that only the anterior pituitary will see. Dopamine is the hormone released into the portal vein between the hypothalamus and anterior pituitary, and it inhibits the cells that make prolactin. Since it is an endocrine signal, it isn't a pathway of the brain. But if you give dopamine antagonists, they could cause galactorrhea and amenorrhea in women and gynecomastia in men.

Parkinson's Disease

Parkinson's disease (PD) is a degenerative disease of the **nigrostriatal dopaminergic system**. The patient progressively loses the substantia nigra (the dopamine machine). The progressive loss of dopamine leads to worsening symptoms. Since **dopamine is movement** and the disease claims the dopamine-secreting cells, the patients present with **less movement**, termed **bradykinesia**. Bradykinesia is characterized by the **mask-like face** (diminished facial expression), **shuffling steps**, a resting **pill-rolling tremor**, and **cogwheel rigidity** (movement is interrupted periodically: normal movement with abrupt pauses). It is important to note that this syndrome is **Parkinson*ism***. Several neurodegenerative diseases and antipsychotic medications can have or cause the syndrome of Parkinsonism—the symptoms—and not be or cause PD.

The presumptive diagnosis of PD can be made if the central triad of Parkinsonism—tremor, rigidity, and bradykinesia— is present in the absence of another etiology. This can be confirmed by symptomatic improvement through dopamine replacement therapy. You are about to learn the characteristic biopsy findings for PD. A brain biopsy is never done to diagnose PD, except on autopsy. **Don't do a brain biopsy for Parkinson's.** An MRI can sometimes demonstrate degeneration of the substantia nigra, but often even the MRI is not necessary.

The first genetic link is the gene that encodes the protein α-synuclein. Aggregates of **α-synuclein** (termed **Lewy bodies**) are the hallmark histological finding in PD. These aggregates are toxic to neurons. They also appear to be released and digested by neighboring neurons, as evidenced by the fact that after the loss of the substantia nigra they spread to contiguous regions of the brain, ascending the brainstem, and can eventually reach the cortex. In patients with PD and not just Parkinsonism, the condition is progressive, eventually claiming the mesolimbic and mesocortical tracts, resulting in personality changes, depression, and, ultimately, dementia.

If a patient presents with severe dementia and progresses to Parkinsonism, the diagnosis is **Lewy body dementia**. If a patient presents with severe Parkinsonism and eventually progresses to dementia, it is **Parkinson's disease**. Both are variants of **α-synuclein** inclusions. Other genes have been implicated, such as those that cause mitochondrial dysfunction (the genes for DJ-1, PINK1, and **parkin**) as well as an autosomal dominant cause of inheritable and severe PD (*LRRK2*). We include them, but the crux of the disease remains Lewy bodies, aggregates of **α-synuclein** inducing the apoptosis of dopaminergic cells.

We go into detail about protein aggregates in Neuroscience: Clinical Cortex #18: *Neurocognitive Degeneration*. We want you to focus on dopamine in this lesson.

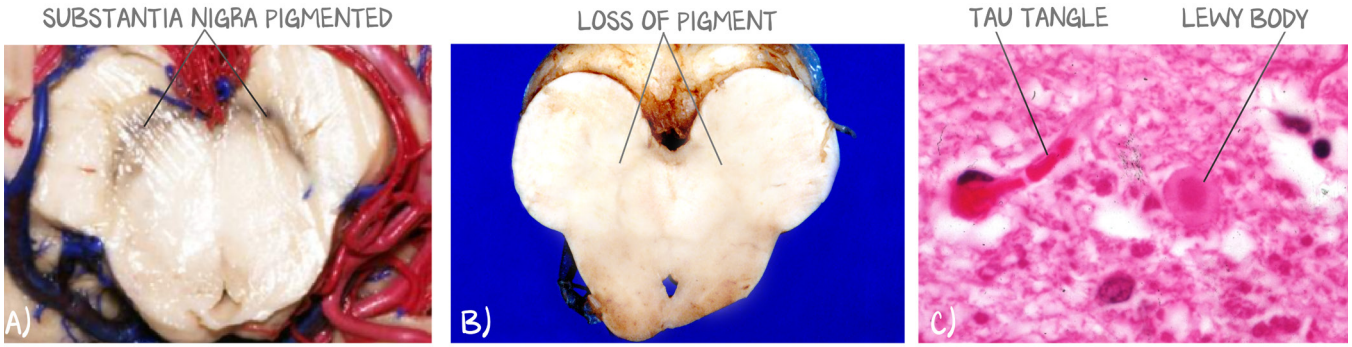

Figure 5.7: Parkinson's Pathology
(a) Normal brainstem showing the dark-appearing substantia nigra, provided for comparison with (b), which shows the complete absence of dark coloration. (c) Lewy body at extremely high magnification, an intracytoplasmic inclusion body of **α-synuclein.** There is also a nearby tau tangle.

Treating Parkinson's

They don't have dopamine, so whatta you do? Give 'em dopamine! Right and wrong. The goal is indeed to **increase dopamine in the nigrostriatal tract**. The goal is to increase dopamine in one area of the brain, but drugs are absorbed by and distributed to all body tissues. Thus, we cannot simply give dopamine, but rather must find a way to get it into the CNS while keeping it away from peripheral receptors. **Dopamine has systemic side effects.** We previously discussed dopamine as a vasopressor and heart rate stimulator. In patients who received dopamine replacement with levodopa, but didn't get carbidopa (more on both in a bit), excess dopamine in the systemic vasculature resulted in anorexia, nausea, and vomiting in almost 80% of patients. Even in the brain, if it activates and overstimulates other dopaminergic tracts that are less affected by the disease, it can provoke **schizophrenia symptoms**—both positive (things that are there but should not be) and negative (the things that should be there but aren't). **Positive symptoms** include delusions, hallucinations, disorganized speech, and disorganized behavior. **Negative symptoms** include flat affect (lack of emotional expression), poverty of speech, poverty of movement, anhedonia, and cognitive delay.

So, treating PD is more complex. You will not be asked, at this stage of training, to choose which medication a patient should receive. There are too many treatment considerations for your level of training. Instead, you will be asked about their mechanisms and, based on the mechanism, what the side effects could be. You should be able to recognize the medications, know their mechanisms, where they work, and what they are supposed to do. Follow along with Figure 5.8.

Levodopa (the medication name) is L-DOPA (the molecule). Levodopa is a pill, taken by mouth. Levodopa is not active, but it is lipophilic and can cross the blood-brain barrier. **Dopamine decarboxylase** (DDC) converts L-DOPA into dopamine. DDC exists in the systemic vasculature and

CNS. The intention is for L-DOPA to cross the blood-brain barrier and be converted into dopamine, activating dopamine receptors. DDC will convert L-DOPA to dopamine wherever DDC finds L-dopa. Dopamine in the bloodstream is toxic. In the brain is where dopamine can have its desired effects. So, to keep DDC at bay, another medication is added—a DDC antagonist, **carbidopa**. Carbidopa cannot cross the blood-brain barrier, so it inhibits DDC in the systemic vasculature, reducing the conversion of L-DOPA into dopamine in the periphery. This means there is more L-DOPA to get into the CNS and less systemic toxicity. The combination of **levodopa/carbidopa** (L-DOPA and DCC inhibitor) is the mainstay of therapy. However, exposure to levodopa will always result in long-term complications. Motor fluctuations, such as the **"wearing-off" phenomenon** (loss of the beneficial effect of the medication before the next dose is administered) and **medication-induced dyskinesia** (involuntary chorea movements), are common problems with levodopa. As the disease progresses, doses increase, and side effects become more common.

But other enzymes can degrade either L-DOPA or dopamine into an inactive metabolite.

Catechol-O-methyltransferase (COMT) degrades L-DOPA into 3-OMD (you don't care what this is, only that it is not L-DOPA or dopamine) in the periphery, and degrades dopamine into 3MT (you don't care about this, either) in the CNS. **COMT inhibitors,** such as tolcapone and entacapone, can be added to drug regimens as a means of **limiting levodopa dose increases** and as an adjunct to prevent the wearing-off effect.

Monoamine oxidase-B (**MAO-B**) degrades dopamine to DOPA-C, but only in the brain. **MAO-B inhibitors**, once used as antidepressants before SSRIs and SNRIs came with a better side effect profile, can still be used as an adjunct to levodopa/carbidopa, with the same indications as COMT inhibitors. Examples include selegiline and rasagiline.

Alternatively, you can administer **dopamine agonists**. The substantia nigra is the source of dopamine, and it is lost. But the D_2 receptors that initiate movement are still present. So by giving dopamine agonists, the metabolism business is bypassed altogether. These are used as first-line therapy for young patients in an attempt to forestall the initiation of levodopa. In elderly patients, levodopa/carbidopa should be started first, and dopamine agonists added as adjuncts to prevent increases in levodopa dosage and the wearing-off effect. Examples are pramipexole and ropinirole (bromocriptine is the original dopamine agonist, but should not be used if the others are available).

Amantadine is not used to treat PD. It was used a long time ago and was one of the first-line agents for younger patients. Once dogma, it now no longer exists in recommendations for PD treatment but lingers in the minds of those who studied Parkinsonism way back when. It persists, however, in guidelines for *managing* PD, both for its historical significance and because it can be used to treat levodopa/carbidopa-induced dyskinesia. It isn't treating the PD, just a side effect of PD treatment.

Anticholinergics are not used to treat PD. Theoretically, since there is an imbalance between stimulatory dopamine and inhibitory acetylcholine, by administering anticholinergic medications, the balance would tip in favor of the "go" signal. Chemically, it is true. But it provides benefit only in patients with prominent tremor or dystonia. The adverse events—such as urinary retention, constipation, tachycardia, and memory impairment—are limiting factors, especially in older patients with dementia. It is never a first-line agent. Benztropine is an example.

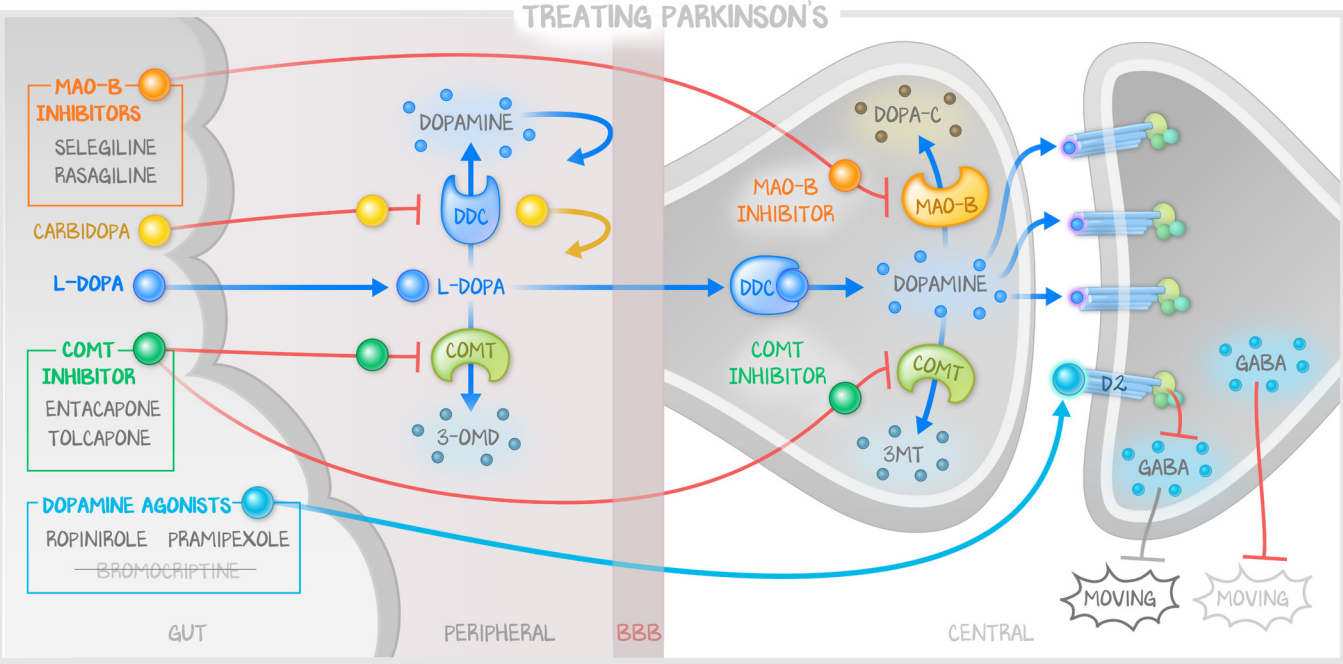

Figure 5.8: Treating Parkinson's
A summary of the preceding section. For those who are young (under 65) with Parkinsonism symptoms, dopamine agonists (ropinirole, pramipexole) are the first line to delay the use of levodopa. Whenever levodopa (L-DOPA) is chosen, the DDC inhibitor carbidopa is chosen with it. All other medications are adjuncts. The goal with both dopamine agonists and carbidopa-levodopa is to disinhibit the thalamus. The activation of D_2 receptors effectively inhibits the release of GABA (an inhibitory neurotransmitter), thereby releasing the thalamus to initiate movement.

Citations

Figures 5.2a, 5.2b, 5.2c: Courtesy of Radiopaedia.

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